UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

6/15/00

MEMORANDUM

SUBJECT: **Vinclozolin:** Common Mechanism of Toxicity of Dicarboximide Fungicides (Chemical I.D. No. 113201, DP Barcode D266718)

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INTRODUCTION

In response to the NRDC comments on the Agency Supplement to the **Vinclozolin** Notice of Filing PP#0F6079 to establish succulent bean and canola tolerances, the Health Effects Division (HED) of EPA's Office of Pesticide Programs is providing the scientific and policy basis to the Registration Division (RD) and the Special Review and Reregistration Division (SRRD) for the OPP decision not to conduct a cumulative risk assessment at this time.

FQPA requires EPA to estimate cumulative risk from all sources of compounds having a common mechanism of toxicity. It should be stressed, however, that HED is moving in a

stepwise fashion to the cumulative assessment of antiandrogenic pesticides.

Vinclozolin, procymidone, and iprodione are members of the imide group of the dicarboximide class of fungicides. There is some evidence that these compounds induce similar toxic effects. Further, all of these fungicides appear to be antiandrogenic. The mechanistic basis for their antiandrogenic properties have been studied to different degrees. There are studies underway at EPA's National Health and Environmental Effects Laboratory to better elucidate the mechanism of toxicity for these antiandrogenic fungicides as well as mixture studies on how they interact. Although all three of these fungicides effectively reduce the level of testosterone, they do so by different pathways. Vinclozolin and procymidone bind and compete for the androgen receptor. Iprodione disrupts the endocrine system by inhibiting androgen synthesis rather than competing for the androgen receptor. It should be noted that these three chemicals do not have any known metabolites/degradates in common with the possible exception of 3,5-dichloroaniline which is structurally and toxicologically different from the parent compounds and unlikely to be antiandrogenic.

The androgen system may be modulated in different ways including competitive binding to androgen receptors, interference with gene control over the synthesis of several enzymes or other factors associated with synthesis of androgen and testosterone. All of these variables relate to the potency, specificity, and site of action of the antiandrogen and determine the expression of the antiandrogenicity induced by various compounds. Because of the complexity of the androgen system, a careful evaluation of all the available data is needed as well as peer review by the FIFRA Science Advisory Panel before a formal decision is made regarding whether or not these compounds modulate androgens by a common mechanism of toxicity. The evaluation of a common mechanism would follow the 1999 EPA Guidance for Identifying Pesticide Chemicals and Other Substances That Have A Common Mechanism of Toxicity (Fed. Reg. 64:5796-5799). Furthermore, procymidone has yet to be subjected to the Reregistration Eligibility Decision (RED) process and, as part of this process, its toxicology database must meet current standards of acceptability. Although there are data suggesting that these dicarboximide fungicides induce some of the same antiandrogenic effects, the mechanism by which they cause these toxic effects have not been adequately evaluated.

Even after an evaluation of all the data and a decision is made regarding a common mechanism of toxicity, other analyses are important to conduct regarding the integration of exposure and hazard data to determine the likelihood that such groupings might result in a cumulative risk as described in the Agency's Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (http://www.epa.gov/scipoly/sap/1999/september/cumdoc.pdf). Only then can it be determined whether there is a need to conduct a cumulative risk assessment on these dicarboximide fungicides.